REMARKS

As the Examiner will note, independent claims 13, 21, and 25, have been amended above to recite, with positive manipulative phraseology, that the method of treatment is performed by "identifying a subject in need of treatment of a pathology affecting the internal tissues of the eye," "topically applying" the growth factor composition to the surface of an eye "to treat the pathology affecting the internal tissues of the eye" of the subject in need thereof, "and treating the pathology affecting the internal tissues of the eye of the subject in need thereof." As discussed below, neither of the references applied in the rejections teach or suggest those positive manipulative steps as now required by all claims. Thus, in view of these amendments, and for the reasons presented below, it respectfully is submitted that the Examiner will find that the claims now clearly distinguish from the art applied and that application is in condition for allowance. Support for the amendment to claims 13, 21, and 25, is found in the claims as previously amended and in the specification at, for example, page 1, lines 4-12, and at pages 18-28.

Claim 17 also has been amended to depend from claim 13 instead of cancelled claim 16.

It is submitted that the amendments to the claims above do not introduce new matter, and entry and approval of the same, respectfully are solicited.

Anticipation Rejections

Claims 13-15, 17-21, and 23-36 were rejected under 35 USC §102(b) as anticipated by Lambiase, WO 98/48002, ("Lambiase '002"). (Paper No. 20060901 at 2-3). For the reasons presented below, reconsideration and withdrawal of this rejection respectfully are solicited.

Lambiase '002 discloses that "nerve growth factor (NGF) is used for the storage of corneas in culture, for the production and the storage *in vitro* of single cell populations of the corneal morphological and functional unit (*i.e.*, epithelium, stroma/keratocytes and endothelium) and of the conjunctival epithelium, and for the production and the storage of corneal and conjunctival tissues, in particular for transplantation purposes." (Abstract). "The NGF is also proposed for use in the therapy and/or the prophylaxis of diseases of the corneal surface, wherein a lack of integrity of the corneal and conjunctival morphological and functional unit occurs, in particular for pathologies having a dystrophic or neurodystrophic basis, both congenital and acquired." (*Id.*).

The Examiner asserted that "[i]t is the examiner's position that, inherently, the composition advanced by [Lambiase] '002, when injected into the eye, treats the same eye-related disorders as the instant application. Since the essential elements of the [Lambiase] '002 composition and method are identical to the instant compositions and methods (that is, injecting a composition comprising 10 to 500 μg/ml of nerve growth factor to an individual), the composition would inherently treat the same disorders as the compositions set forth in the instant application. As such, it is the examiner's position that the

composition advanced by [Lambiase] '002 anticipates the compositions enumerated in the instant claim set." (*Id.* at 3).

In response to Applicant's remarks submitted March 8, 2006, the Examiner asserted that "the methods of treating eyes with NGF advanced by both Lambiase and Finkenaur would treat the same internal tissues of the eye as set forth in the instant claim set. Since the essential elements of the Lambiase and Finkenaur compositions and methods are identical to the instant compositions and methods ..., the composition would inherently treat the same disorders as the compositions set forth in the instant application." (*Id.* at 4-5). The Examiner further asserted that "[s]ince the essential elements of the methods appear to be the same, the internal tissues to be treated would also necessarily be the same." (*Id.* at 5).

As is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). ***Each and every element*** recited in a claim must be found in a single prior art reference and ***arranged as in the claim***. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.,* 221 USPQ 481, 485 (Fed. Cir 1984). ***There must be no differences*** between what is claimed and what is disclosed in the applied reference. *In re Kalm*, 154 USPQ 10, 12 (CCPA 1967); *Scripps v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). "Moreover, it is incumbent upon the Examiner to ***identify wherein each and every facet*** of the claimed invention is disclosed in the applied reference." *Ex parte Levy*, 17

USPQ2d 1461, 1462 (BPAI 1990). The Examiner is required to point to the disclosure in the reference "***by page and line***" upon which the claim allegedly reads. *Chiong v. Roland*, 17 USPQ2d 1541, 1543 (BPAI 1990).

Turning to the method of treatment recited in all of the claims as amended, as is clear, each claim positively requires the steps of:

(1) identifying a subject in need of treatment of a pathology affecting internal tissues of the eye;

(2) topically applying a growth factor composition to treat the pathology affecting the internal tissues of the eye; and

(3) treating the subject in need of treatment of a pathology affecting the internal tissues of the subject's eye.

As is apparent, Lambiase does not disclose or suggest (1) identifying a subject in need of treatment of a pathology affecting internal tissues of the eye; (2) ***topically applying a growth factor composition to treat the pathology affecting the internal tissues of the eye***; and (3) treating the subject in need of treatment of a pathology affecting the internal tissues of the subject's eye. So, whether or not Lambiase's composition is the same as the composition recited in the claims, is irrelevant. As a matter of fact Lambiase does not teach or suggest the combination of manipulative steps required by all claims. As a matter of law, therefore, Lambiase does not anticipate any of the claims.

Lambiase '002 discloses treating pathologies affecting the ***surface*** of the eye (*i.e.*, cornea and conjunctiva) by administration of the "composition" on

the eye surface or treating pathologies of the ***internal*** tissues of the eye by administration of the "composition" ***into the eyeball by injection*** -- not by topical application.

Applicant's claimed method is concerned with the administration of the composition (*e.g.*, in the form of eye-drops) "over an ocular surface," which composition is able to pass through the ocular tissues and reach the internal tissues, so that it does not need at all to be injected *in situ*, not even to treat pathologies affecting the internal tissues of the eye. *See* specification, at page 6, line 18 to page 9, line 5. It is clear that Lambiase '002 only concerns applying the product to the damaged site as opposed to the claimed invention, which is entirely based on the unexpected finding that NGF is able to ***pass through the ocular tissues***, so that, in order to treat internal ocular tissues, the product need only be applied onto the ocular surface, *i.e.*, it does not need to be directly applied onto the affected site (wound).

If an ophthalmologist had to apply the "teachings" of Lambiase in order to treat affected internal tissues, after formulating a diagnosis of affection of some internal tissues of the eye, he/she would have had to inject the NGF composition *in situ*. However, according to the instant invention, as it has been now discovered that NGF is able to pass from the external tissues (cornea and conjunctiva) to the internal tissues of the eye, the claimed method only requires applying NGF as, for example, eye-drops on the external surface of the eye. NGF will penetrate to the affected internal tissues and exert its therapeutic action on the affected tissues. Therefore, the method of treatment claimed involves

using an administration route, in relation to the affection detected, which is different from and not disclosed by Lambiase. In this regard, the specification as filed contains numerous examples of the diagnosis steps that precede the application of the claimed method of treatment (an affection of the sclera, the ciliary bodies, the crystalline lens, the retina, the vitreous body or the choroidea). (See Specification at pages 18-28). Accordingly, for this additional reason, the rejection should be withdrawn.

We further note that the Examiner asserted "*inherently*, the composition advanced by [Lambiase] '002, when injected into the eye, treats the same eye-related disorders as the instant application." The Examiner's only assertion to support this inherency theory is that "[s]ince the essential elements of the Lambiase ... compositions and methods are identical to the instant compositions and methods ..., the composition would inherently treat the same disorders as the compositions set forth in the instant application." (Paper No. 20060901 at 4-5). This is absolutely insufficient to demonstrate inherency. An examiner must provide rationale or evidence tending to show inherency, not mere speculation. *See* MPEP § 2112 (8th ed., Rev. 5, Aug. 2006, at p. 2100-47) ("The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)."). This, the

Examiner has ***simply*** not done (and for the second time). For this additional reason, the rejection should be withdrawn.

Furthermore, the Examiner's assertion to support inherency (*i.e.*, "[s]ince the essential elements of the Lambiase ... compositions and *methods are identical* to the instant compositions and methods ..., the composition would inherently treat the same disorders as the compositions set forth in the instant application.") is ***factually wrong***. (Paper No. 20060901 at 4-5). As discussed above, the Lambiase '002 method ***only concerns*** applying the product to the damaged site ***as opposed to the claimed method of treatment***, which is entirely based on the unexpected finding that NGF is able to ***pass through the ocular tissues***, so that, in order to treat internal ocular tissues, the product need only be applied onto the ocular surface, *i.e.*, it does not need to be directly applied onto the affected site (wound) like the method disclosed in Lambiase.

The rejection is also, again, devoid of any discussion of claims 14-15, 17-21, and 23-36, separate from claim 13. Accordingly, the record is devoid of any evidence that the Examiner individually considered claims 14-15, 17-21, and 23-36. It is axiomatic, however, that each claim is to be examined on its own merits. It is also axiomatic that a dependent claim is not *per se* anticipated by prior art that anticipates the base claim. Accordingly, "[e]xaminers are reminded that a dependent claim is directed to a combination including everything recited in the base claim and what is recited in the dependent claim. ***It is this combination that must be compared with the prior art, exactly as if it were presented as one independent claim.***" MPEP § 608.01(n) (8th ed. Rev. 5, Aug.

2006, p. 600-91). This the Examiner has not done. Accordingly, the rejection is both factually and legally deficient as to claims 14-15, 17-21, and 23-36. For this additional reason, the rejection should be withdrawn as to claims 14-15, 17-21, and 23-36.

Claims 13-15, 18-19, 21, 24-28, and 30-36 were rejected under 35 USC §102(b) as anticipated by Finkenaur *et al.*, EPA 0312208A1 ("Finkenaur"). (Paper No. 20060901 at 3). For the reasons set forth below, the rejection, respectfully is traversed.

Finkenaur discloses that "[g]el formulations containing polypeptide growth factors having human mitogenic or angiogenic activity are provided. The gel formulations are useful for topical or incisional ***wound*** healing for cutaneous wounds, in the anterior chamber of the eye and other ophthalmic wound healing." (Abstract.)

In making the rejection, the Examiner asserted that Finkenaur "disclose aqueous gel formulations comprising 1 to 500 μg/ml of a polypeptide growth factor, such as nerve growth factor (abstract and page 3, lines 25- 48). Said nerve growth factor can be used for wound healing in the anterior chamber of the eye (abstract). Said wound healing composition can be delivered to an individual via a bandage (page 2, lines 49-50)." (Paper No. 20060901 at 3).

The Examiner then asserted that "[i]t is the examiner's position that, inherently, the composition advanced by [Finkenaur], when injected into the eye, treats the same eye-related disorders as [t]he instant application. Since the essential elements of the '208 composition and method are identical to the

instant compositions and methods (that is, injecting a composition comprising 1 to 500 μg/ml of nerve growth factor to an individual), the composition would inherently treat the same disorders as the compositions set forth in the instant application. As such, it is the examiner's position that the composition advanced by [Finkenaur] anticipates the compositions enumerated in the instant claim set." (*Id.* at 3-4).

In response to Applicant's remarks submitted March 8, 2006, the Examiner asserted that "the methods of treating eyes with NGF advanced by both Lambiase and Finkenaur would treat the same internal tissues of the eye as set forth in the instant claim set. Since the essential elements of the Lambiase and Finkenaur compositions and methods are identical to the instant compositions and methods ..., the composition would inherently treat the same disorders as the compositions set forth in the instant application." (*Id.* at 4-5). The Examiner further asserted that "[s]ince the essential elements of the methods appear to be the same, the internal tissues to be treated would also necessarily be the same." (*Id.* at 5).

Initially, we note, *again*, particularly in view of the fact that this case has been transferred to *another* Examiner,[1] that Finkenaur was considered and applied in the first Office Action (Paper No. 6 at p. 3) in a 35 U.S.C. § 102(b) rejection by previous Examiner L. Di Nola Baron. After reviewing our Response filed March 27, 2003, previous Examiner L. Di Nola Baron withdrew the rejection

[1] This patent application has been transferred to *three* different Examiners since 2003.

in its entirety. The Examiner conceded that Finkenaur fails to "**teach [a] formulation administered [to] the ocular surface of the eye.**" (*See* Paper No. 9 at 4-5) (emphasis added). Finkenaur was *again* considered and applied in a 35 U.S.C. § 103(a) rejection by previous Examiner L. Di Nola Baron in a Final Office Action mailed May 20, 2003. (*Id.*). And again, after reviewing our Response filed November 20, 2003, the Examiner withdrew the rejection in its entirety. (*See* Paper No. 20031223 at 8). In other words, the disclosure of Finkenaur has already been considered and applied by the PTO ***twice***. In view of the arguments made, the PTO ***conceded twice*** that Finkenaur does not disclose the method claimed and is not a bar to patentability under either §102 or §103. For this reason alone, the current rejection, being based on the same disclosure, should be withdrawn.

In view of the foregoing, we respectfully remind the Examiner that "[p]iecemeal examination should be avoided as much as possible. ***The examiner ordinarily should reject each claim on all valid grounds available.***" MPEP § 707.07(g), 8th ed., Rev. 5, Aug. 2006, p. 700-128).

In the interest of saving time, we incorporate by reference our previous arguments with respect to Finkenaur as if recited in full herein. Just as before, these arguments alone are sufficient to overcome the rejection.

We also note that the Examiner again has failed to acknowledge or address the limitation "wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues" in claims 13, 21, and 25 (from which claims 14-15 and 17-20, 23-24, and 26-36 depend, respectively).

The Examiner also failed to acknowledge or address the range limitation of 200 to 500 μg/ml in claim 25 (and dependent claims 26-36).

Having failed to address these limitations, the Examiner failed to identify where in Finkenaur each and every element of claims 13, 21, and 25 are shown. That, however, was the Examiner's burden. Accordingly, the rejection is insufficient as a matter of law and fact to support a conclusion of anticipation, and for this reason alone, the rejection should be withdrawn with respect to claim 13 (and dependent claims 14-15 and 17-20) and claim 21 (and dependent claims 23-24), and claim 25 (and dependent claims 26-36).

Furthermore, it is respectfully submitted that the Examiner has misinterpreted the disclosure of Finkenaur. Finkenaur is discussed at p. 5 of applicant's specification. The specification states:

> With specific reference to the disorders affecting ***the exposed ocular surface***, i.e. corneal and conjunctival diseases, EP-A-0312208 discloses gel formulations for use in the treatment of epithelial lesions and epithelial pathologies in general, including lesions and pathologies of the ocular surface. The said formulations contain an active ingredient which may be indiscriminately chosen among the various molecules whose name contains the expression "growth factor". Although ***the description is exclusively concerned with the epidermal growth factor (EGF)*** as the preferred active ingredient, and although activity data (*in vitro*) and formulation examples are given only for EGF, other growth factors are mentioned as well, such as FGF (fibroblast growth factor), PDGF (platelet-derived growth factor), TGF-α (transforming growth factor) or the NGF itself. The said growth factors are apparently presented as a family of molecules having equivalent characteristics and biological activity as EGF. As a matter of fact, at the current state of the knowledge, ***it is undisputed***

> ***that the said growth factors have different specific targets and that they often have conflicting effects, so that they are not considered as biologically equivalent to each other.*** (emphasis added).

The various growth factors mentioned above are different individual molecules, with a different amino acid sequence, structure and molecular weight, and, above all, different receptor sites and different biological activity. For instance, EGF is a 53 amino acid polypeptide having a molecular weight of about 6000 dalton, while NGF is a 140 kdalton molecular complex. ***The present claims recite a method based on NGF. Finkenaur only incidentally mentioned NGF and does NOT disclose the method currently claimed.***

Finkenaur teaches the use of EGF for the treatment of incisional wounds, based on the disclosed mitogenic properties of this compound. (See p. 2, lines 17-24). Finkenaur discloses the direct application of the product on a wound, whether it be a surface wound or an internal wound. (See p. 4, lines 7-32). It is clear that Finkenaur concerns applying the product to the damaged site/wound as opposed to the claimed invention, which is entirely based on the unexpected finding that NGF is able to ***pass through the ocular tissues***, so that, in order to treat internal ocular tissues, the product need only be applied onto "the ocular surface," *i.e.*, it is not directly applied onto the affected site (wound).

The Examiner asserted that Finkenaur discloses that "nerve growth factor can be used for wound healing in the anterior chamber of the eye

(abstract)" and "[s]aid wound healing composition can be delivered to an individual via a bandage [placed on the wound] (page 2, lines 49-50)." (Paper No. 20060901 at 3). The method of treatment claimed, however, recites that the treatment occurs by administering "over an ocular surface." As discussed above, Finkenaur discloses direct application of the composition on the wound. For example, Finkenaur discloses "soak[ing] a bandage [with a formulation to be] ***placed on the wound***." (Page 2, line 50). Thus, the rejection does not – and cannot – identify where in Finkenaur it is disclosed to administer "over an ocular surface" and "wherein said nerve growth factor passes through the external tissues of said eye to said internal tissues." Indeed, the PTO has conceded that Finkenaur fails to "**teach [a] formulation administered [to] the ocular surface of the eye**." (*See* Paper No. 9 at 4-5) (emphasis added). Because Finkenaur does not disclose each and every element arranged as recited in the claimed method, it does not anticipate any pending claims. Thus, the rejection is factually and legally deficient and should be withdrawn.

We further note that the Examiner asserted "*inherently*, the composition advanced by [Finkenaur], when injected into the eye, treats the same eye-related disorders as [t]he instant application." The Examiner's only assertion to support this inherency theory is that "[s]ince the essential elements of the ... Finkenaur compositions and methods are identical to the instant compositions and methods ..., the composition would inherently treat the same disorders as the compositions set forth in the instant application." (Paper No. 20060901 at 4-5). As discussed above, this is absolutely insufficient to

demonstrate inherency. An examiner must provide rationale or evidence tending to show inherency, not mere speculation. *See* MPEP § 2112 (8th ed., Rev. 5, Aug. 2006, at p. 2100-47) ("The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)."). This, the Examiner has ***simply*** not done (and for the second time). For this additional reason, the rejection should be withdrawn.

Furthermore, the Examiner's assertion to support inherency (*i.e.*, "[s]ince the essential elements of the ... Finkenaur compositions and *methods are identical* to the instant compositions and methods ..., the composition would inherently treat the same disorders as the compositions set forth in the instant application.") is ***factually wrong***. (Paper No. 20060901 at 4-5). As discussed above, the Finkenaur method ***only concerns*** applying the product to the damaged site/wound ***as opposed to the claimed method of treatment***, which is entirely based on the unexpected finding that NGF is able to ***pass through the ocular tissues***, so that, in order to treat internal ocular tissues, the product need only be applied onto "the ocular surface," *i.e.*, it is not directly applied onto the affected site (wound) like the method disclosed in Finkenaur.

Thus, the Finkenaur method does not disclose "[a] method for the treatment of a pathology affecting internal tissues of an eye" by "administration of

a composition comprising ... nerve growth factor over an ocular surface of a subject in need thereof, wherein said nerve growth factor passes through external tissues of said eye to said internal tissues ..." as claimed. Therefore, Finkenaur does not disclose each and every element recited in the ***method*** claimed. *Marshall*, 198 USPQ at 346; *Lindemann Maschinenfabrik,* 221 USPQ at 485. For this additional reason, the anticipation rejection should be withdrawn.

The rejection is also, again, devoid of any discussion of claims 14-15, 17-21, and 23-36, separate from implicitly discussing claim 13. Accordingly, the record is devoid of any evidence that the Examiner individually considered claims 14-15, 17-21, and 23-36. It is axiomatic, however, that each claim is to be examined on its own merits. It is also axiomatic that a dependent claim is not *per se* anticipated by prior art that anticipates the base claim. Accordingly, "[e]xaminers are reminded that a dependent claim is directed to a combination including everything recited in the base claim and what is recited in the dependent claim. ***It is this combination that must be compared with the prior art, exactly as if it were presented as one independent claim.***" MPEP § 608.01(n) (8th ed. Rev. 5, August 2006, pp. 600-91). This the Examiner has not done. Accordingly, the rejection is both factually and legally deficient as to claims 14-15, 17-21, and 23-36. For this additional reason, the rejection should be withdrawn as to claims 14-15, 17-21, and 23-36.

In view of the foregoing, favorable action on the merits, including entry of the amendment, withdrawal of the rejections, and allowance of all the

claims, are respectfully requested. If the Examiner has any questions regarding this paper, please contact one of the undersigned attorneys.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on February 6, 2007.

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